Results: The optimal signature contained 28 genes. There was a statistically significant correlation between actual versus predicted time to recurrence for blind data (rho = 0.975; $p < 0.0001$). A prospective Kaplan–Meier plot was generated which showed no significant difference to the actual Kaplan–Meier plot for this dataset ($p > 0.955$).

Discussion: For the first time gene expression signatures have been identified that predict actual time to event data rather than placing patients into arbitrary risk groups. Coupled with the ability to derive prospective Kaplan–Meier plots, this tool has the potential for assessing prognosis and determining treatment regimens on a case by case basis.

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O-34 DYNAMIC CONTRAST-ENHANCED MRI REVEALS CORE SIGNALLING PATHWAYS IN BREAST CANCER

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Dynamic contrast-enhanced MRI (DCE-MRI) is a widely used imaging modality for the management of breast cancer patients. At present, there is little understanding of how imaging patterns on DCE-MRI relate to the molecular pathways that drive tumour growth.

To address this issue, we performed a retrospective study of 65 patients with primary breast cancer, for whom pre-treatment DCE-MRI scans and formalin fixed paraffin embedded (FFPE) core biopsies were available. We used pharmacokinetic modelling of DCE-MRI to quantify the rate constant k_{ep} governing contrast agent washout from the tumour extravascular extracellular space. By computing the median k_{ep} over tumour volume an overall tumour leakiness score was derived. We extracted RNA from FFPE cores and measured gene expression using Affymetrix Human Plus 2.0 arrays. Following normalization and pre-processing, we used permutation tests to determine which genes were significantly correlated with median k_{ep}. Pathway analysis was performed using GeneCodis with the KEGG database.

Setting the False Discovery Rate to 5% resulted in 1258 genes that were significantly positively correlated with tumour leakiness including integrins B1 and A6, TGFBR1, HIF1 and 2A, SMAD4, HES1, JAG1. Interestingly, pathway analysis revealed that the p53 ($P < 0.004$), Wnt ($P < 0.004$) and Notch signalling pathways ($P < 0.006$), which are known to have important roles in angiogenesis, were all significantly associated with tumour leakiness.

These results illustrate how the combination of non-invasive imaging and gene expression profiling can reveal the molecular correlates of radiological features and provide insight into the mechanisms driving tumour growth and angiogenesis.

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O-35 SERPINB3, A BIOMARKER OF TAXANE BENEFIT IN BREAST CANCER

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Background: Lysosomal cathepsin proteases function in a programmed cell death (LPCD) pathway. Although there is evidence for the importance of this pathway in cancer cell survival, it has not been exploited in anti-cancer therapeutics. Hsp70 and serpinB3 can block this pathway and promote cell survival. Furthermore, serpinB3 is associated with lack of response to chemotherapy. Cathepsin mediated cell death is observed in response to anthracyclines or taxanes, which are widely utilised in breast cancer treatment.

Methods: We evaluated serpinB3 and Hsp70 by immunohistochemistry in 255 surgically resected breast tumours from patients treated with either CVAP or CVAP and docetaxel prior to potentially curative resection. The study was performed with the approval of the regional research ethics committee.

Results: SerpinB3 and Hsp70 were significantly correlated with poor pathological response ($P = 0.014$ and $P < 0.0001$, respectively). SerpinB3 positivity is a poor prognostic factor ($P = 0.029$; mean survival 88.8 vs. 100.4 months) and this is independent in multivariate analysis ($P = 0.023$). Patients with serpinB3 positive tumours have poor survival if treated with anthracycline ($P = 0.026$) but not if they are also given a taxane ($P = 0.786$). Furthermore, only patients with serpinB3 positive tumours benefit from taxane treatment ($P = 0.008$).

Conclusions: SerpinB3 and Hsp70 are predictive biomarkers, potentially blocking breast tumour response to chemotherapy by preventing LPCD. SerpinB3 is prognostic and may prevent anthracycline-, but not taxane-, mediated cytotoxicity in breast tumours. Patients with serpinB3 negative tumours have a good prognosis when treated with anthracycline-based therapy alone. In contrast, patients with serpinB3 positive tumours benefit significantly from the addition of docetaxel.

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O-36 RECRUITMENT OF INSULIN RECEPTOR SUBSTRATE-1 BY ErbB3 IMPACTS ON IGF-IR SIGNALLING IN OESTROGEN RECEPTOR-POSITIVE BREAST CANCER CELLS

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We have shown that insulin receptor substrate 1 (IRS-1) can associate with epidermal growth factor receptor (EGFR), with activation of EGFR promoting recruitment and phosphorylation of IRS-1 in an oestrogen receptor (ER)-positive tamoxifen resistant breast cancer (BC) cell line. In this study, we examined recruitment of IRS-1 by another erbB receptor family member, erbB3 in three ER-positive BC cell lines. Our studies revealed an interaction